PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 March 2001 (20.03.01)	
International application No. PCT/EP00/06917	**Applicant's or agent's file reference** L/XI83/ems/7
International filing date (day/month/year) 17 July 2000 (17.07.00)	**Priority date** (day/month/year) 16 July 1999 (16.07.99)
Applicant KRENNING, Eric, Paul et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   07 February 2001 (07.02.01)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Claudio Borton

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
L/XI83/ems/7		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06917	17/07/2000	16/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant MALLINCKRODT, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/02/2001	27.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ludwig, G Telephone No. +49 89 2399 8698

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06917

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17	as originally filed

Claims, No.:

1-20	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4, 6-7, 9-14, 16-17, 19-20.

because:

☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-4, 6-7, 9-14, 16-17, 19-20 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Reference is made to the following document/s/:

D1: Br. J. Cancer 67, 1437-1439 (1993)
D2: J. Nucl. Med. 829-833, 37 (1996)

1. Documents D1 and D2 disclose the use of combinations of lysine and arginine for inhibiting renal uptake of Indium-labelled somatostatin and Tc-labelled monoclonal antibody fragments, respectively.

   Claims 5 and 15 are therefore not regarded as novel vis-a-vis these documents and nothing inventive can be seen in claims 8 and 18 in view of them.

2. For the assessment of the present claim 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item III:

3. The passage in claims 1 and 11, i.e. "or an amino acid or other proteinaceous moiety having a free amino group with a pK *substantially similar or equal* to that of lysine" is so broad and vague that it is not known which compounds are intended.

   The passage in claims 1 and 11, i.e. "a positively charged compound" is so broad and encompasses a plethora of completely different compounds that it is not known which compounds are intended.

4. Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

PATENT COOPERATION TREATY

PCT

10/031509

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
L/XI83/ems/7		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 06917	17/07/2000	16/07/1999
Applicant		
MALLINCKRODT, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   INHIBITION OF RENAL UPTAKE OF RADIOMOLECULES WITH A COMBINATION OF LYSINE AND ARGININE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,6,7,9-14,16,17,19,20

Present claims relate to an extremely large number of possible uses/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the uses/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful complete search over the whole of the claimed scope is impossible.
Moreover the claims relate to compounds which are actually not well-defined, namely "other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine or salts or carboxyl derivatives thereof" and " a second compound which is a positively charged compound or salts or carboxyl derivatives thereof" The claims cover all uses/compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such uses/compounds, namely referring to peptides that are coupled to radionuclides or metals. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the combination/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the uses/compounds disclosed in the examples and the compounds specifically identified by chemical name in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K47/48 A61K51/06 A61P35/00 A61K51/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAMMOND P J ET AL: "Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue" BRITISH JOURNAL OF CANCER,GB,LONDON, vol. 67, June 1993 (1993-06), pages 1437-1439, XP002105271 ISSN: 0007-0920 page 1437, column 2 abstract --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2001	01/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BEHR T M ET AL: "REDUCTION OF THE RENAL UPTAKE OF RADIOLABELED MONOCLONAL ANTIBODY FRAGMENTS BY CATIONIC AMINO ACIDS AND THEIR DERIVATIVES" CANCER RESEARCH,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD,US, vol. 55, no. 17, 1 September 1995 (1995-09-01), pages 3825-3834, XP000946492 ISSN: 0008-5472 see discussion page 3832, column 1, paragraph 1; figure 7 page 3830, column 1 ---	1-20
X	WO 91 04755 A (NEORX CORP) 18 April 1991 (1991-04-18) page 9, line 17-27 page 13; claims 1,5 ---	1-20
X	PIMM M V ET AL: "Prevention of renal tubule re-absorption of radiometal (indium-111) labelled Fab fragment of a monoclonal antibody in mice by systemic administration of lysine" EUROPEAN JOURNAL OF NUCLEAR MEDICINE,DE,BERLIN, vol. 21, no. 7, July 1994 (1994-07), pages 663-665, XP002105272 ISSN: 0340-6997 page 663, column 1, paragraph 2 page 665, paragraph 2 ---	1-20
X	BEHR T. M. ET AL: "Reduction of renal uptake of monoclonal antibody fragments by aminoacid infusion" J. NUCL. MED., vol. 37, no. 5, May 1996 (1996-05), pages 829-833, XP000978766 see discussion abstract; table 1 ---	1-20
Y	KRENNING E. P. ET AL: "Radiolabelled somatostatin analogue(s) for peptide receptor scintigraphy and radionuclide therapy" ANNALS OF ONCOLOGY, vol. 10, no. Suppl 2, 1999, pages s23-s29, XP000978221 page S28, column 1; figure 1 --- -/--	1-20

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International Application No
PCT/EP 00/06917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BEHR T. M.; GOLDENBERG D. M.: "Improved prospects for cancer therapy with radiolabeled antibody fragments and peptides?" J. NUCL. MED., vol. 37, no. 5, May 1996 (1996-05), pages 834-836, XP000978767 page 834, column 3; figure 1 ---	1-20
A	WO 97 46099 A (NEORX CORP) 11 December 1997 (1997-12-11) claims 10,11 ---	1-20
Y	WO 96 29087 A (MOLECULAR MEDICINE CENTER) 26 September 1996 (1996-09-26) claims 1-3; example 5 ---	1-20
A	EP 0 747 395 A (CLINTEC NUTRITION CO) 11 December 1996 (1996-12-11) page 4, line 5-30 page 2, line 32-34 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9104755 A	18-04-1991	AT 136224 T	15-04-1996
		CA 2066031 A	30-03-1991
		DE 69026387 D	09-05-1996
		DE 69026387 T	28-11-1996
		EP 0494247 A	15-07-1992
		JP 5500953 T	25-02-1993
		US 5648059 A	15-07-1997
		US 5380513 A	10-01-1995
WO 9746099 A	11-12-1997	CA 2257353 A	11-12-1997
		EP 0906015 A	07-04-1999
WO 9629087 A	26-09-1996	US 5843894 A	01-12-1998
		AU 700346 B	07-01-1999
		AU 5361696 A	08-10-1996
		CA 2190867 A	26-09-1996
		EP 0767673 A	16-04-1997
		JP 10505866 T	09-06-1998
EP 0747395 A	11-12-1996	US 5728678 A	17-03-1998
		CA 2177195 A	07-12-1996
		JP 9020678 A	21-01-1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05383 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/EP00/06917

(22) International Filing Date: 17 July 2000 (17.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/144,106 16 July 1999 (16.07.1999) US

(71) Applicant *(for all designated States except US)*: **MALLINCKRODT, INC.** [US/US]; 675 McDonnell Boulevard, St. Louis, MO 63134 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KRENNING, Eric, Paul** [NL/NL]; Hoflaan 71, NL-3062 JC Rotterdam (NL). **DE JONG, Marion** [NL/NL]; Eleonorstraat 119, NL-3135 PA Vlaardingen (NL). **VALKEMA, Roelf** [NL/NL]; Louise de Colignylaan 28, NL-2341 CK Oegstgeest (NL).

(74) Agent: **VAN SOMEREN, Petronella, Francisca, Hendrika, Maria**; Arnold & Siedsma, Sweelinckplein 1, NL-2517 GK The Hague (NL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05383 A2

(54) Title: INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY

(57) Abstract: The invention relates to the use of the combination of a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof, for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys, and that are used for therapeutical or diagnostic purposes. The combination consists advantageously of lysine and arginine.

INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY

The present invention relates to the inhibition of renal uptake of molecules that are potentially damaging for the kidney.

Radionuclide labeled peptides and also monoclonal antibodies or their fragments and other compounds like certain antibiotics undergo undesired renal uptake and cellular retention leading to a high kidney dose, or concentration. In the case of diagnosis or therapy with radiolabeled proteinaceous compounds, like peptides and monoclonal fragments, the uptake of these compounds by the kidneys leads to a reduction in the detection sensitivity of perirenal tumors or an increase in kidney radiotoxicity.

In certain other situations a general overload of proteins in the kidney can occur, such as in the case of amino acid metabolism diseases, induced catabolism or prolonged physical exercise, e.g. long-distance running.

Increased amounts of protein or raised doses of radiation or toxic substances in the kidneys may eventually lead to kidney damage.

International patent application No. WO91/04755, filed September 24, 1990, teaches methods to reduce non-target kidney retention of immunoconjugates, metabolites thereof, including other substances, such as peptides, by coadministration of a non-target moiety, such as lysine, or other amino acids having a free amino group. The application discloses only experimental results with mice showing that higher doses of lysine as a non-target reduction moiety improved results, i.e. the percentage of the injected immunoconjugate dose detected in the kidney is decreased. However, no information is provided concerning the possible toxicity of the method, and no data in humans were supplied. It is a known fact that there are differences in the physiology, including the renal physiology between mice and humans.

Additionally, it is known that infusion of amino acid solutions can induce side effects, including hyperkalemia (e.g. Ponce SP, et al. Medicine 64: 357-370, 1985, and Sartori S, et al. Recenti Progressi in Medicina 82(6): 275-277, 1991). This has been reported in particular for arginine (e.g. Massara F, et al. Diabete et Metabolisme 5(4):297-300, 1979), but it is also known in general medical practice for lysine, among others (Speck SP. in: Rakel RE, ed. Saunders Manual of Medical Practice; W.B. Saunders Company, Philadelphia, 2000, pp 885-888).

It is furthermore a known practice to use in patients an infusion of commercially available cocktails of various amino acids to lower the uptake of radiolabeled pharmaceuticals such as [^{111}In-DTPA-D-Phe^{1}]octreotide in the kidney (Hammond et al. in Br. J. Cancer 67, 1437-1439 (1993), Barone R, et al., J. Nucl. Med, 41: 94P (2000)). Such cocktails usually comprise a total amount of about 100 grams or more of various amino acids. In order to keep the osmolarity of such mixed amino acid solutions tolerable for human infusion, the total volume will be in the range of 2 liters.

This type of treatment has the observed disadvantageous side-effect that patients may suffer from severe vomiting, presumably caused by toxicity of the high total amount of amino acids administered. Additionally, the infusion of any volume of 2 liters within 4 hours, especially when it is hyperosmolar, can be dangerous to patients with impaired cardiac or renal function.

For the purpose of the invention, i.e. inhibiting renal uptake, it is necessary to reach a particular serum level of amino acids within a relatively short time, because excretion of the bulk of radiopharmaceuticals occurs within the first 4 to 6 hours after administration. During this time the radiopharmaceuticals may be taken up by the kidneys. It is thus not possible to avoid the side-effect of vomiting

by administering the amino acid cocktail over a longer period of time.

Furthermore, it has been described by De Jong et al. in J. Nucl. Med 37(8): 1388-1392 (1996) that uptake in the rat kidneys of the [^{111}In-DTPA-D-Phe^{1}]octreotide can be inhibited by 50% by intravenous administration of the amino acid L-lysine alone (400 mg/kg). In a further article by Bernard et al. in J. Nucl. Med. 38: 1929-1933 (1997) it was demonstrated that also D-lysine is capable of reducing the rat renal uptake of [^{111}In-DTPA-D-Phe^{1}]octreotide and ^{90}Y-DOTA,Tyr^{3}-octreotide.

However, treatment with lysine has also various disadvantages. It was for example found in humans that L-lysine in an effective total dose of 75 g (see examples for details) may lead to severe hyperkalemia which may result in acute and life-threatening cardiotoxicity in 50% of the patients.

In WO96/29087 it is also suggested to reduce kidney uptake of antibody fragment conjugates by administration of lysine or poly-lysine. It is taught in said application that toxicity of lysine can be avoided by using D-lysine because it does not occur naturally in humans or animals and is believed to be metabolically inert, thereby reducing the risk of toxic side-effects associated with the use of L-lysine. The prescribed dosage of monomeric lysine in this application is 1-200 g. The examples do not give results of treatments with humans with lysine alone. The only experiments in humans are performed with the commercially available amino acid solution Periamin X^{TM}. According to the invention it is now shown that even 75 g of lysine is too high a dose. This already indicates that WO96/29087 may mention, but does not really enable the use of lysine in humans.

From the prior art it thus follows that reduction of renal uptake of unwanted proteinaceous materials can be achieved by either the use of amino acid cocktails that are commonly used as parenteral food

supplements or with lysine alone. Either method has however the disadvantage that it may lead to toxic effects in humans.

It is therefore the object of the invention to provide a new improved way of inhibiting the renal tubular uptake of various types of proteinaceous molecules, such as proteins, peptides and antibodies.

This is achieved by the invention by the use of the combination of:

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and
- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof,

for the preparation of a composition for inhibiting renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes.

Preferred positively charged compounds are amino acids, e.g. arginine, ornithine or citrulline. The preferred positively charged amino acid for use together with lysine is arginine.

It was found that 50% inhibition in renal uptake of [^{111}In-DTPA-D-Phe^{1}]octreotide in rats could be achieved by D-Lysine or L-lysine at 400 mg/kg. L-arginine alone gave a reduction of 20-30% at an equimolar dose. In human studies 15, 21 and 40% reduction of kidney uptake of [^{111}In-DTPA-D-Phe^{1}]octreotide was reached using a dose of 25, 50 and 75 g L-lysine, respectively. The doses of 25 and 50 g L-lysine were well tolerated without any toxicity noted, but the 75 g L-lysine dose was associated with severe hyperkalemia in 50% of the patients. Hyperkalemia may result in acute and life-threatening cardiotoxicity.

The combination of L-lysine and L-arginine, however, shows a synergistic effect and is more effective

than both compounds alone at equimolar concentrations in reducing renal uptake of radiolabeled peptides. Using the combination, lower doses of the two amino acids can therefore effectively inhibit the (radio)pharmaceutical renal uptake and simultaneously prevent hyperkalemia and cardiotoxicity. The normal serum potassium values lie between 3.5 and 5.3 mmol/L. Values between 5.3 and 6.0 mmol/L are a grey area. Values above 6.0 mmol/L are not acceptable, and cardiotoxicity may occur.

An additional advantage of the use of the two compounds of the invention is that the total infusion volume can be kept to 1 liter, which is safer than 2 liter in patients with compromised renal or cardiac function.

The treatment of the invention was found to have a lower impact on the increase in potassium level in serum than a treatment with 75 g lysine in 1500 mL. Whereas in the latter case 3 out of 6 patients had a maximum potassium level above the critical value of 6.0 mmol/L, the treatment of the invention resulted in only one out of eleven patients having a maximum potassium value of 6.0 mmol/L.

It is assumed that a possible mechanism of action of the invention is based on a blockade of megalin, a type I membrane glycoprotein of 4630 amino acids, 600 kDa, and having a pI of 4.6 that mediates renal tubular reabsorption. Megalin's mechanism of action is based on endocytosis through coated pit vesicles. Megalin transports positively charged molecules and is found on the brush border of proximal tubular cells, thyroid follicular cells, parathyroid cells, in the mammary gland, placenta, yolk sac and on lung type II pneumocytes.

The inhibition of renal uptake of proteins and peptides can be effected during therapy and diagnosis to protect the kidneys from detrimental side-effects of the therapeutic or diagnostic materials. In addition, when tissues surrounding the kidneys are subjected to

localization with radiolabeled proteins or peptides, renal uptake of these radioactive materials may interfere with the scintigraphic visualization due to radiation from the kidneys that obscures the radiation from these surrounding tissues. Inhibition of accumulation of radioactivity in the kidneys is then also desirable.

It was also found according to the invention that after treatment with the combination of L-lysine plus L-arginine during radiotherapy with [^{177}Lu-DOTA,Tyr^3] octreotate none of the 11 patients treated suffered from vomiting. In contrast, with the treatment with a cocktail of several amino acids (see examples for the details) 42% of the patients vomited who received radiotherapy with ^{90}Y-DOTA,Tyr^3-octreotide. In 45% of these patients vomiting was very severe, i.e. 5 to 30 times. In another experiment it was found that in only 8% of treatments with the L-lysine and L-arginine combination vomiting occurred, mainly observed in one single patient, and this were probably not related to this combination.

The invention is suitable for inhibiting the renal uptake of all sorts of proteinaceous materials, such as proteins, peptides and monoclonal antibodies or their fragments. Renal uptake is to be avoided in case the proteinaceous materials are inherently toxic for the kidneys, and when they are coupled to a toxin, a radionuclide, a cytostatic agent or other potentially detrimental product. Renal uptake of nephrotoxic antibiotics or cytostatic agents per se is also to be prevented. In some cases the uptake by the kidneys of other, non-detrimental proteins can also be a problem. Protein is metabolized by the liver and excreted by the kidneys into the urine. A high protein load causes damage to these organs. In addition, diseases related to amino acid metabolism could lead to a protein overload in the kidneys.

Specific examples of diagnosis and therapies in which the composition of the invention could be used to inhibit or prevent renal uptake of the diagnostic or

therapeutic agent are the use of radiolabelled peptides, including but not limited to octreotide and other somatostatin analogs, labelled with ^{111}In, ^{90}Y, ^{177}Lu, ^{131}I or any other suitable radionuclide. Further examples are the diagnostic and therapeutic application of monoclonal antibodies or their fragments, nephrotoxic drugs such as antibiotics and cytostatic drugs.

In all these and other situations, the inhibition of the uptake of proteins or pharmaceuticals by the kidneys according to the invention can be beneficial.

The invention further relates to therapeutical compositions for inhibiting the renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes, which composition comprises one or more suitable excipients, carriers or diluents and a combination of

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and
- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

Preferred positively charged compounds are amino acids, e.g. arginine, ornithine or citrulline. The preferred positively charged amino acid for use together with lysine is arginine.

In a preferred embodiment of the composition it comprises lysine and arginine. The amount of lysine in the composition is between 10 and 45 grams, preferably between 15 and 35 grams, more preferably between 20 and 30 grams, most preferably about 25 grams. The amount of arginine is between 15 and 45 grams, preferably between 15 and 35 grams, more preferably between 20 and 30 grams, most preferably about 25 grams. Such amounts are preferred for administration in 1 L over 4 hours.

Preferably the total amount of the two compounds does not exceed 100 grams, is preferably less than 75 grams and is more preferably not more than 50 grams. The amounts given are intended for adults. For children the usual modifications can be made.

In this application the term "first compound" should be understood to refer to one or more members selected from the group consisting of lysine, poly-lysine, pharmaceutically acceptable salts or carboxyl derivatives thereof, as well as amino acids or other proteinaceous moieties having a free amino group with a pKa substantially similar or equal to that of lysine. The "second compound" is to be understood to refer to one or more positively charged compounds, preferably selected from among positively charged amino acids, more preferably selected from among arginine, ornithine and citrulline or poly-amino acids or pharmaceutically acceptable salts or carboxyl derivatives of the positively charged amino acids. The preferred combination is such that the first compound is lysine, which may be either D-lysine, L-lysine or poly-lysine. The second compound is preferably arginine, which may be either D-arginine, L-arginine or poly-arginine.

The therapeutical composition of the present invention can be in an oral or parenteral dosage form. Parenteral dosage forms include intravenous, intraarterial, intraperitoneal, intramuscular and subcutaneous dosage forms, preferably intravenous dosage forms. Administration may be via a single or via multiple boluses, or by continuous or discontinuous infusion and is preferably by continuous infusion over 4 hours, starting about 30 minutes prior to administration of the radiopharmaceutical.

The combination of compounds of the present invention may be administered in any pharmaceutically acceptable solution. A solution is said to be pharmaceutically acceptable if its administration can be tolerated by a recipient patient. Sterile phosphate-

buffered saline is one example of a pharmaceutically acceptable carrier, as is Ringer lactate, Hartman's solution or a mixture of glucose and saline. Other suitable carriers are well-known to those skilled in the art.

The present invention will be further illustrated in the examples that follow and that are not intended to limit the scope of the invention.

In the examples reference is made to the following figures:

Figure 1 shows the ratio between [^{111}In-DTPA-D-Phe^1]octreotide uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours). Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

Figure 2 shows the ratio between [^{177}Lu-DOTA, Tyr^3]octreotate uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours). Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

Figure 3 shows the ratio between [^{111}In-DTPA-D-Phe^1]octreotide uptake in various organs in the presence or absence of 1 L glucose/saline solution, administered over 4 hours. Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

Figure 4 shows between [^{111}In-DTPA-D-Phe^1]octreotide uptake in the left kidney after a 0.5 + 3.5 hour infusion of various amino acid compositions.

EXAMPLES

MATERIALS

Composition of infusion fluids

A. Lys/Arg

Combination of L-lysine and L-arginine (total 1000 mL)

- L-arginine HCl 10% 250 mL (=25 grams of L-arginine)
- L-lysine HCl 5% 500 mL (=25 grams of L-lysine)
- HCl 25% is added to achieve pH 7.4
- NaCl 0.9% is added to achieve a total volume of 1000 mL

The osmolarity of this combination is ca. 400 mosmol/L
The total quantity of amino acids is 50 grams.

B. Cocktail of various amino acids (total 2030 mL)

- Aminosteril N-Hepa 8% 1500 mL
- Ringer lactate 500 mL
- Magnesium sulfate (7-water) 10% 30 mL

The osmolarity of this combination is ca. 700 mosmol/L
The total quantity of amino acids is 124.5 grams.

Aminosteril N-Hepa 8% is a commercially available solution containing a mixture of amino acids (Fresenius AG, Gluckensteinweg 5, D-6380 Bad Homburg v.d. H., Germany). The composition is given herein below.
Ringer lactate is a mineral solution containing NaCl 0.6%, $CaCl_2.2H_2O$ 0.04%, Na-lactate 0.322% (Baxter B.V., Energielaan 3, NL-5405 AD Uden, The Netherlands)

Composition of Aminosteril N Hepa 8% infusion fluid

SUBSTANCE	QUANTITY (g/L)		Total in 1500 mL	
L-isoleucine	10,40		15,600	
L-leucine	13,09		19,635	
L-lysinemonoacetate (= 6,88 g L-lysine)	9,71	(6.88)	14,565	(10.32)
L-methionine	1,10		1,650	
Acetylcysteine (= 0,52 g L-cysteine)	0,70	(0.52)	1,050	(0.78)

L-fenylanaline	0,88	1,320
L-treonine	4,40	6,600
L-tryptophane	0,70	1,050
L-valine	10,08	15,120
L-arginine	10,72	16,080
L-histidine	2,80	4,200
Aminoacetic acid (glycine)	5,82	8,730
L-alanine	4,64	6,960
L-proline	5,73	8,595
L-serine	2,24	3,360
Acetic acid	4,42	
Total amino acids	**83,01 g/L**	**124,52 grams**
Total nitrogen	12,90 g/L	
Osmolarity	**770 mosm/L**	**770 mosm/L**

C. L-Lysine (total 500 mL) per unit

- L-lysine HCl 5% 500 mL (=25 grams of L-lysine)
- HCl 25% is added to achieve pH 7.4

The osmolarity of this solution is ca. 400 mosmol/L

For 50 grams of L-lysine 2 units (total 1000 mL) are used; for 75 grams of L-lysine 3 units (1500 mL). Saline (NaCl 0.9%) or a mixture of glucose and saline (NaCl 0.45% + glucose 2.5%), can be added to increase the infusion volume.

All these infusion fluids are given over a period of 4 hours, with a maximum of 2.03 L per 4 hours. The rate of infusion can be constant over 4 hours, but initial high rates of infusion followed by lower rates of infusion are employed also. These infusion fluids can be given for periods up to 12 hours, with maximal average infusion rates of 2.03 L per 4 hours.

EXAMPLE 1

Effect of intravenous Lysine/Arginine infusion on tissue uptake

A 1000 mL infusion containing 25 g L-lysine and 25 g L-arginine (**Lys/Arg**; see MATERIALS, paragraph A. for

exact formulation) was administered intravenously to patients during 4 hours, starting 30 minutes prior to administration of the radioligand. One radioligand was [^{111}In-DTPA-D-Phe^{1}]octreotide (^{111}In-pentetreotide, OctreoScan®, Mallinckrodt Medical, Petten, The Netherlands) in a diagnostic amount of 220 MBq (9 patients). Each patient was also investigated on a separate occasion with 220 MBq ^{111}In-pentetreotide, but without any infusion. The other radioligand was [^{177}Lu-DOTA,Tyr^{3}]octreotate in a therapeutic amount of 1850 MBq (5 patients). Each patient was also investigated on a separate occasion with 1850 MBq [^{177}Lu-DOTA,Tyr^{3}]-octreotate, but without any infusion. The control experiment (5 patients) consisted of infusion of 1000 mL neutral infusion fluid without the amino acids (NaCl 0.45% plus Glucose 2.5%)over 4 hours, starting 30 min. prior to the injection of 220 MBq ^{111}In-pentetreotide.

24 Hours post infusion the uptake of the radioligand in the kidneys, spleen and liver was measured using planar scintigraphy and dosimetry, and for each patient the ratio between uptake in these organs during infusion with **Lys/Arg** and without **Lys/Arg** was calculated (Figures 1, 2 and 3).

In the 9 patients who received a diagnostic dose of 220 MBq of ^{111}In-pentetreotide, during **Lys/Arg** infusion the mean uptake of the radioligand in the kidneys was reduced to 68% (left) and 52% (right) of their own control without **Lys/Arg** (Figure 1).

In the 5 patients who received a therapeutic dose of 1850 MBq [^{177}Lu-DOTA,Tyr^{3}]octreotate, during **Lys/Arg** infusion the mean uptake of the radioligand in the kidneys was reduced to 63% (left) and 61% (right) of their own control without **Lys/Arg** (Figure 2).

The control experiment showed no significant differences in renal uptake of ^{111}In-pentetreotide whether 1000 mL of (neutral) infusion fluid was administered or not, thus ruling out the infusion volume itself as a contributing factor to reduce renal uptake of ^{111}In-

pentetreotide (Figure 3).

From these combined results it follows that there is a 40% decrease of ^{111}In-pentetreotide or [^{177}Lu-DOTA,Tyr^3]octreotate uptake in the kidneys during **Lys/Arg** infusion as compared to the control.

EXAMPLE 2

Effect of Lys/Arg infusion on serum potassium levels

In an experiment of the invention 11 patients received an infusion over 4 hours of a solution containing 25 g L-lysine and 25 g L-arginine in 1000 mL (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation). The potassium level of these patients was measured in serum at t=0 hours and after 0.5, 1, 2, 4 and 5 hours. The results are shown in table 1 and figure 4.

Table 1
Potassium level in serum during infusion of 1000 mL Lys/Arg over 4 hours, starting 30 min. prior to the administration of ^{111}In-pentetreotide in a diagnostic amount of 220 MBq.

patient no.	0	0.5	1	2	4	5	max. difference
1	4.6	4.6	4.9	5.4	5.5	5.4	0.9
2	4.2	4.1	4.6		4.8		0.7
3	4.3	4.5	4.7	4.9	5.4	4.8	1.1
4	4.5	4.7	5.3	**6.0**	5.7		1.5
5	4.5	4.5		5.0	5.3		0.8
6	4.1	4.2		5.1	5.2	5.3	1.1
7	4.4	4.1		4.5	5.0		0.6
8	3.7	3.3		3.9	4.5	4.4	0.8
9	3.0	3.0		3.6	4.0		1
10	4.3	4.3		4.8	5.5		1.2

11	4.5	n.d.	4.4	4.9	4.8		0.4
Average	4.2	4.1	4.8	4.8	5.1		0.9

As a control 6 patients received 75 g L-lysine in 1500 mL during 4 hours (see MATERIALS, paragraph C. for exact formulation). Their maximum serum potassium levels are given in Table 2.

Table 2
Maximum potassium level in serum during infusion of 75 g L-lysine in 1500 mL over 4 hours, starting 30 min. prior to the administration of ^{111}In-pentetreotide in a diagnostic amount of 220 MBq (patients 12, 13, 14, 15), or in a therapeutic amount of 7 GBq (patients 16, 17).

patient	maximum potassium (K) level
12	5.2
13	**6.8**
14	**6.7**
15	5.4
16	5.0
17	**6.3**

Patient no. 17 showed transient muscle weakness, the other patients had no symptoms related to the infusion.

EXAMPLE 3

Effect of different amino acid preparations on [^{111}In-DTPA]octreotide uptake in the kidney

At least 5 patients received one of the following amino acid preparations:

1. AA (2030 mL cocktail of various amino acids; see MATERIALS, paragraph B, for the source and details)

2. 25 g L-lysine in 500 mL (see MATERIALS, paragraph C, for exact formulation)
3. 50 g lysine in 2000 mL (see MATERIALS, paragraph C, for exact formulation)
4. 75 g lysine in 1500 mL (see MATERIALS, paragraph C, for exact formulation)
5. 25 g L-lysine and 25 g L-arginine in 1000 mL (invention), (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation).

The preparations were given intravenously over 4 hours starting 30 minutes before treatment with the radioligand started. The radioligand was ^{111}In-pentetreotide, either in a diagnostic amount of 220 MBq, or in a therapeutic amount, 7 - 11 GBq. Each patient was his or her own control. The control consisted of treatment with the radioligand but without an amino acid preparation.

At 24 and 48 hours post infusion the ratio between tissue uptake in the left kidney in patients receiving an amino acid composition and the controls was determined by planar scintigraphy and dosimetry.

Figure 4 gives the results of this study, which also includes the data obtained in patients described in examples 1 and 2. Although 75 g L-lysine leads to the highest uptake reduction, it was found that it resulted in severe hyperkalemia (Table 2). No hyperkalemia was found in the second best amino acid composition comprising 25 g L-lysine plus 25 g L-arginine (Table 1). Moreover, it was found that more patients vomited that received the AA compositions than patients receiving L-lysine or Lys/Arg(see also EXAMPLES 4, 5, 6).

EXAMPLE 4

Effect of prior art amino acid composition on vomiting

26 patients received 1 to 5 therapeutic doses of 1-10 GBq ^{90}Y-DOTA,Tyr^3-octreotide, with concomitant infusion of a 2030 mL cocktail of various amino acids in

4 hours, starting 30 min. before the administration of the radiopharmaceutical (see MATERIALS, paragraph B. for exact details). In 11 of these 26 patients (42%), [being 20 of 84 treatments (24%)] one or more episodes of vomiting occurred, up to 30 episodes of severe vomiting per treatment.

In one of these 11 patients the vomiting was so severe during the 2 treatments with the above described regimen, that it was decided to use an infusion with 50 g of L-lysine instead of the infusion with the cocktail of various amino acids concomitant with his 3rd and 4th therapy with ^{90}Y-DOTA,Tyr^3-octreotide. Only one episode of vomiting occurred after his 3rd treatment and no vomiting at all after his 4th treatment.

EXAMPLE 5

Effect of lysine on vomiting

8 patients received multiple therapeutic doses of 7-11 GBq ^{111}In-pentetreotide. All received once a concomitant infusion of a 2030 mL cocktail of various amino acids in 4 hours, starting 30 min. before the administration of the radiopharmaceutical (see MATERIALS, paragraph B. for exact details). In 4 of these 8 patients (50%) vomiting occurred.

In these same 8 patients only 3 episodes (9%) of vomiting occurred during 22 treatments with 7-11 GBq ^{111}In-pentetreotide while they received 25 or 50 grams of L-lysine in 500 to 2000 mL (see MATERIALS, paragraph C. for exact details) over 4 hours, starting 30 min. before administration of the radiopharmaceutical, as concomitant infusions.

In these same 8 patients only 3 episodes (6%) of vomiting occurred during 52 treatments while they received no concomitant infusion at all.

EXAMPLE 6

Effect of **Lys/Arg** on vomiting

In an experiment of the invention 11 patients received an infusion over 4 hours of a solution containing 25 g L-lysine and 25 g L-arginine in 1000 mL (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation). Thirty min. after the start of the infusion they received a diagnostic dose of 220 MBq ^{111}In-pentetreotide. Ten patients had no symptoms during the infusion, in particular no vomiting. One patient had subfebrile temperature, malaise and nausea already before the start of the infusion, presumably caused by tumor necrosis. During the **Lys/Arg** infusion she vomited twice. This patient has tolerated the **Lys/Arg** infusion without any problems on all 4 later occasions, while receiving a therapeutic dose of 10-11 GBq ^{111}In-pentetreotide.

Five patients received the **Lys/Arg** infusion in the same manner as described above, but they received a therapeutic dose of 1850 MBq [^{177}Lu-DOTA,Tyr^3]octreotate, 30 min. after the start of the **Lys/Arg** infusion. None of these 5 patients had any symptoms at all, in particular no vomiting.

Until now the **Lys/Arg** infusion, 1000 mL in 4 hours concomitant with therapeutic doses of radioactive labelled peptides, has been administered to more than 30 patients, in total more than 80 occasions. Vomiting occurs in less than 5% of the occasions, and if it occurs it is most probably due to other causes.

From these studies described in EXAMPLES 4, 5 and 6 it was concluded that the infusion of 2030 mL containing a cocktail of various amino acids causes frequent vomiting, which is unacceptable for routine clinical circumstances. On the other hand, vomiting is seldomly observed either with L-lysine infusions or with **Lys/Arg** infusion.

CLAIMS

1. Use of the combination of:

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and

- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof,

for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys, and that are used for therapeutical or diagnostic purposes.

2. Use as claimed in claim 1, wherein the positively charged second molecule is a positively charged amino acid, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

3. Use as claimed in claim 2, wherein the positively charged amino acid is selected from the group consisting of arginine, ornithine and citrulline, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

4. Use as claimed in claims 1-3, wherein the first compound is lysine selected from D-lysine, L-lysine or poly-lysine.

5. Use as claimed in claims 1-4, wherein the first compound is lysine and the second compound is arginine.

6. Use as claimed in claims 1-5, wherein the amount of the first compound is 10-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

7. Use as claimed in claims 1-6, wherein the amount of the second compound is 15-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

8. Use as claimed in claims 1-7, wherein the first compound is lysine in an amount of about 25 grams and the second compound is arginine in an amount of about 25 grams per treatment.

9. Use as claimed in claims 1-8, wherein the two compounds are administered in about 1 L infusion fluid over a period of about 4 hours.

10. Use as claimed in claims 1-9, wherein the substances that may be damaging to the kidneys, and of which the renal tubular uptake is to be inhibited are proteins, peptides or monoclonal antibodies, in particular proteins, peptides or monoclonal antibodies that are inherently toxic, that are coupled to a radionuclide, a cytostatic agent, a toxic agent, a metal, or a combination thereof, or cytostatic agents and nephrotoxic antibiotics per se.

11. Therapeutical composition for the inhibition of the renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys and that are used for therapeutical or diagnostic purposes, which composition comprises one or more pharmaceutically acceptable excipients, carriers or diluents and a combination of

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and
- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

12. Therapeutical composition as claimed in claim 11, wherein the positively charged second molecule is a positively charged amino acid, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

13. Therapeutical composition as claimed in claim 12, wherein the positively charged amino acid is selected from the group consisting of arginine, ornithine

and citrulline, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

14. Therapeutical composition as claimed in claims 11-13, wherein the first compound is lysine selected from D-lysine, L-lysine or poly-lysine.

15. Therapeutical composition as claimed in claims 11-14, wherein the first compound is lysine and the second compound is arginine.

16. Therapeutical composition as claimed in claims 11-15, wherein the amount of the first compound is 10-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

17. Therapeutical composition as claimed in claims 11-16, wherein the amount of the second compound is 15-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

18. Therapeutical composition as claimed in claims 11-17, wherein the first compound is lysine in an amount of about 25 grams and the second compound is arginine in an amount of about 25 grams per treatment.

19. Therapeutical composition as claimed in claims 11-18, wherein the two compounds are present in about 1 L infusion fluid.

20. Method for inhibiting the renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes, in a subject, which method consists of the administration of a therapeutical composition as claimed in claims 11-19.

Figure 1

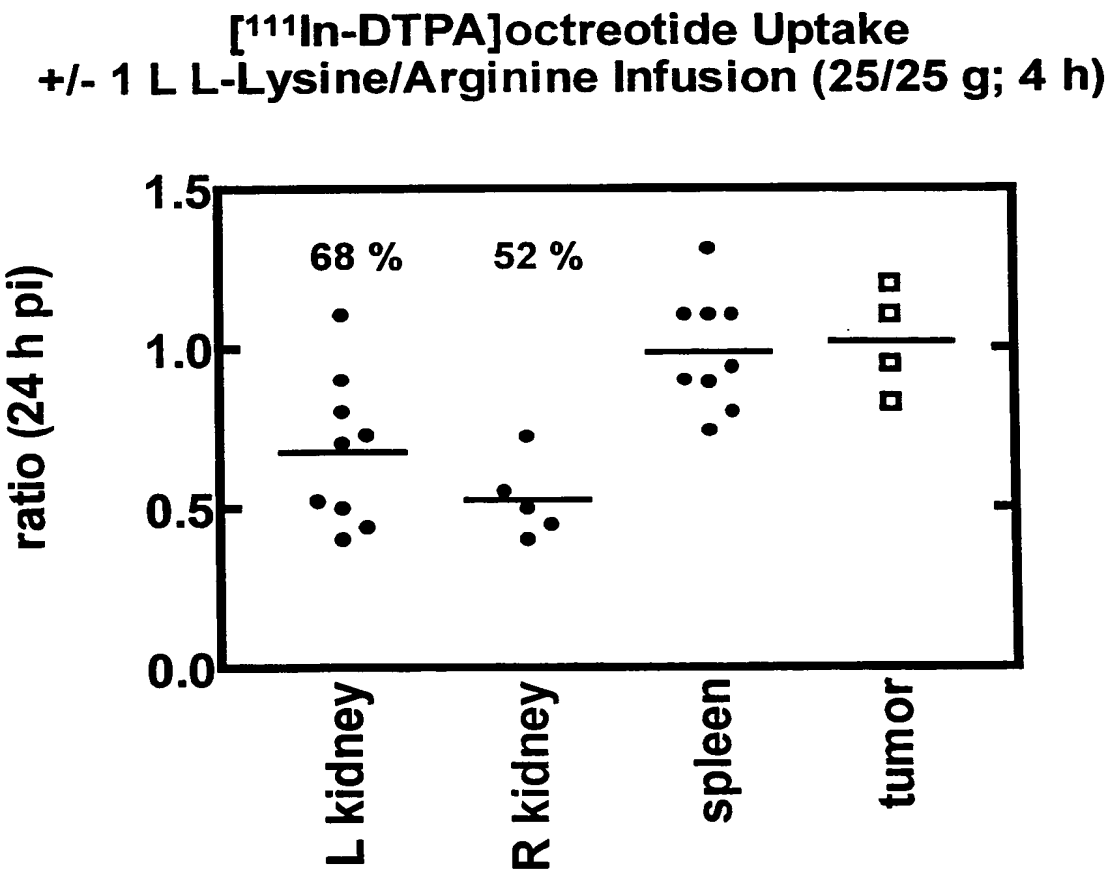

[111In-DTPA]octreotide Uptake
+/- 1 L L-Lysine/Arginine Infusion (25/25 g; 4 h)
ratio (24 h pi)
1.5
1.0
0.5
0.0
68 %
52 %
L kidney
R kidney
spleen
tumor

Figure 2

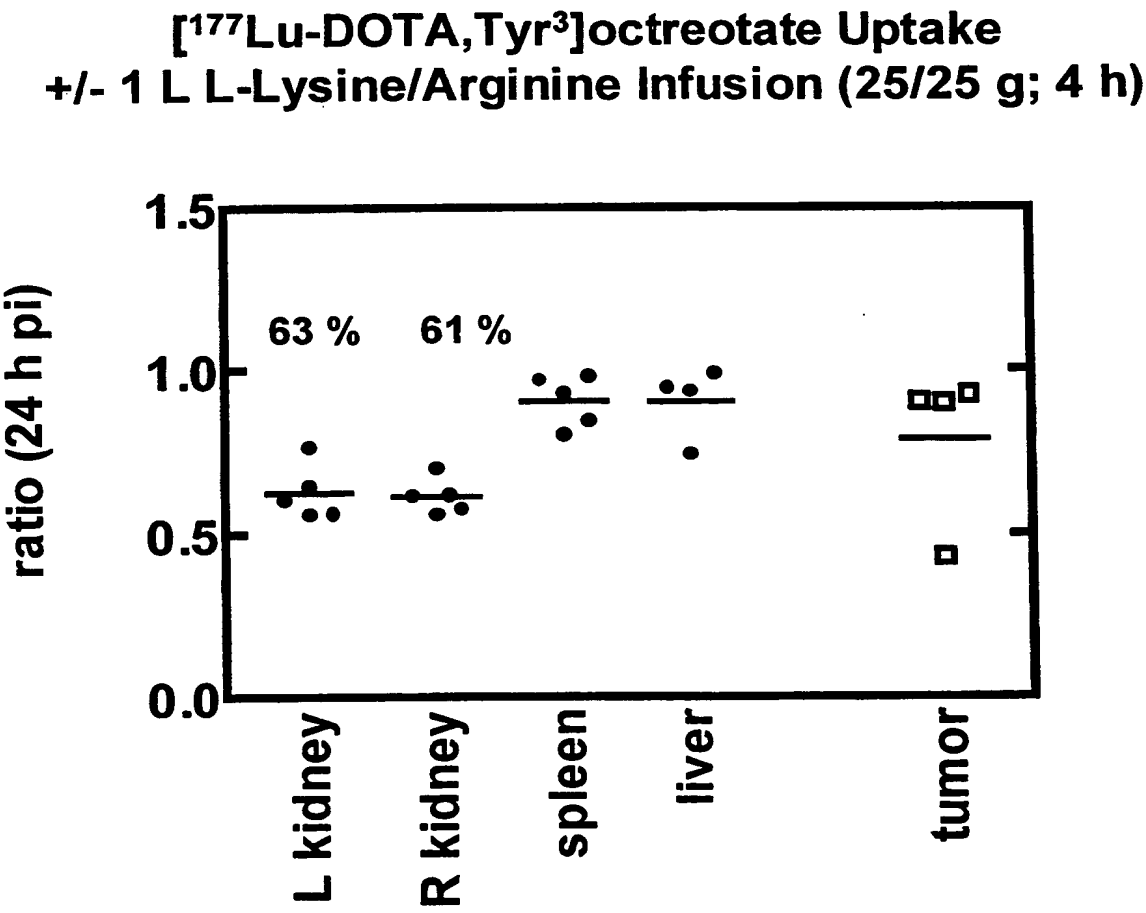

[177Lu-DOTA,Tyr3]octreotate Uptake
+/- 1 L L-Lysine/Arginine Infusion (25/25 g; 4 h)
ratio (24 h pi)
1.5
1.0
0.5
0.0
63 %
61 %
L kidney
R kidney
spleen
liver
tumor

Figure 3

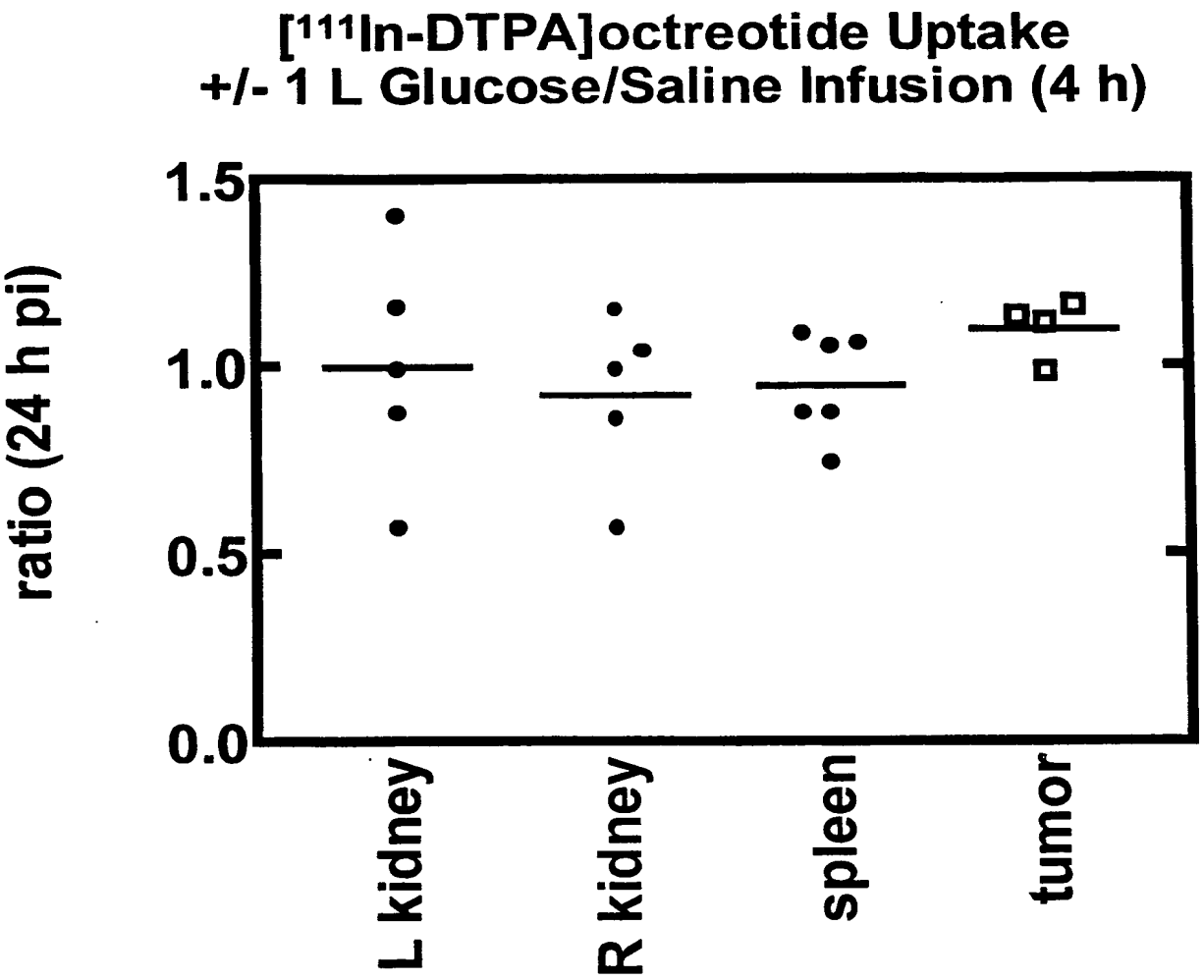
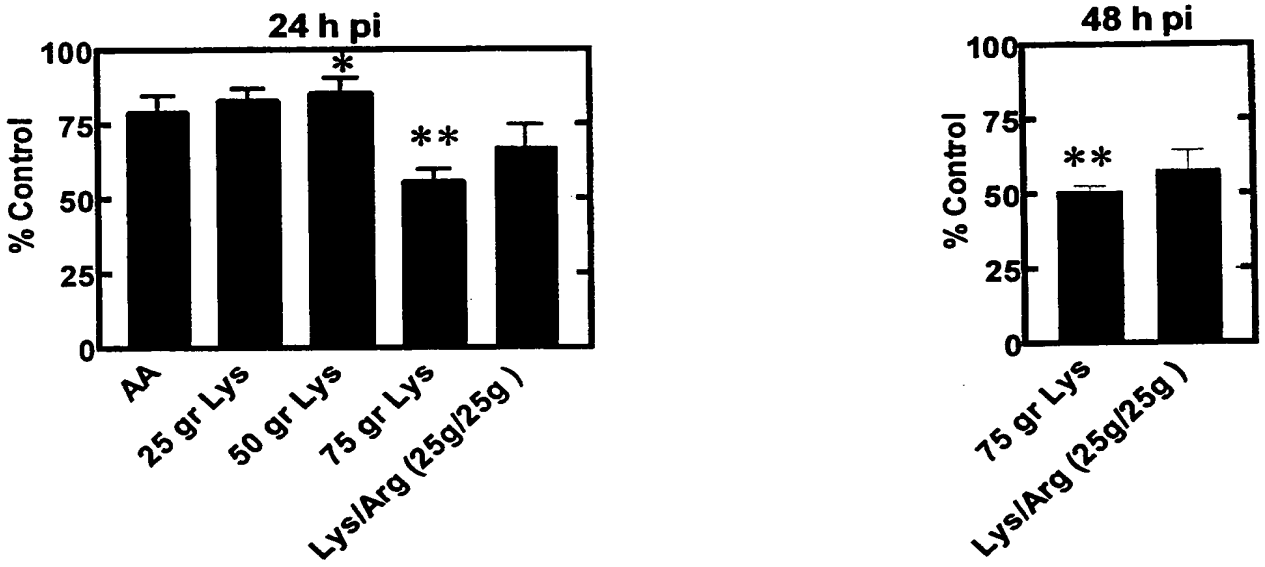

[111In-DTPA]octreotide Uptake
+/- 1 L Glucose/Saline Infusion (4 h)
ratio (24 h pi)
1.5
1.0
0.5
0.0
L kidney
R kidney
spleen
tumor

Figure 4

[^{111}In-DTPA]octreotide Uptake in Left Kidney Effect of 0.5 + 3.5 h AminoAcid Infusion



Versus Lys/Arg (25g/25g): * $p < 0.04$, ** $p > 0.10$

M ± SEM; N ≥ 5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05383 A3

(51) International Patent Classification[7]: A61K 31/195, 47/48, 51/06, A61P 35/00, A61K 51/08

(21) International Application Number: PCT/EP00/06917

(22) International Filing Date: 17 July 2000 (17.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/144,106 16 July 1999 (16.07.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
19 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05383 A3

(54) Title: INHIBITION OF RENAL UPTAKE OF RADIOMOLECULES WITH A COMBINATION OF LYSINE AND ARGININE

(57) Abstract: The invention relates to the use of the combination of a first compound which is lysine, or an amino acid or ther proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts r carboxyl derivatives thereof, and a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof, for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys, and that are used for therapeutical or diagn stic purposes. The combination consists advantageously f lysine and arginine.

INTERNATIONAL SEARCH REPORT

[redacted] onal Application No
[redacted] EP 00/06917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K47/48 A61K51/06 A61P35/00 A61K51/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAMMOND P J ET AL: "Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue" BRITISH JOURNAL OF CANCER,GB,LONDON, vol. 67, June 1993 (1993-06), pages 1437-1439, XP002105271 ISSN: 0007-0920 page 1437, column 2 abstract --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2001	01/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BEHR T M ET AL: "REDUCTION OF THE RENAL UPTAKE OF RADIOLABELED MONOCLONAL ANTIBODY FRAGMENTS BY CATIONIC AMINO ACIDS AND THEIR DERIVATIVES" CANCER RESEARCH,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD,US, vol. 55, no. 17, 1 September 1995 (1995-09-01), pages 3825-3834, XP000946492 ISSN: 0008-5472 see discussion page 3832, column 1, paragraph 1; figure 7 page 3830, column 1 ---	1-20
X	WO 91 04755 A (NEORX CORP) 18 April 1991 (1991-04-18) page 9, line 17-27 page 13; claims 1,5 ---	1-20
X	PIMM M V ET AL: "Prevention of renal tubule re-absorption of radiometal (indium-111) labelled Fab fragment of a monoclonal antibody in mice by systemic administration of lysine" EUROPEAN JOURNAL OF NUCLEAR MEDICINE,DE,BERLIN, vol. 21, no. 7, July 1994 (1994-07), pages 663-665, XP002105272 ISSN: 0340-6997 page 663, column 1, paragraph 2 page 665, paragraph 2 ---	1-20
X	BEHR T. M. ET AL: "Reduction of renal uptake of monoclonal antibody fragments by aminoacid infusion" J. NUCL. MED., vol. 37, no. 5, May 1996 (1996-05), pages 829-833, XP000978766 see discussion abstract; table 1 ---	1-20
Y	KRENNING E. P. ET AL: "Radiolabelled somatostatin analogue(s) for peptide receptor scintigraphy and radionuclide therapy" ANNALS OF ONCOLOGY, vol. 10, no. Suppl 2, 1999, pages s23-s29, XP000978221 page S28, column 1; figure 1 ---	1-20

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BEHR T. M.; GOLDENBERG D. M.: "Improved prospects for cancer therapy with radiolabeled antibody fragments and peptides?" J. NUCL. MED., vol. 37, no. 5, May 1996 (1996-05), pages 834-836, XP000978767 page 834, column 3; figure 1	1-20
A	WO 97 46099 A (NEORX CORP) 11 December 1997 (1997-12-11) claims 10,11	1-20
Y	WO 96 29087 A (MOLECULAR MEDICINE CENTER) 26 September 1996 (1996-09-26) claims 1-3; example 5	1-20
A	EP 0 747 395 A (CLINTEC NUTRITION CO) 11 December 1996 (1996-12-11) page 4, line 5-30 page 2, line 32-34	1-20

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,6,7,9-14,16,17,19,20

Present claims relate to an extremely large number of possible uses/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the uses/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful complete search over the whole of the claimed scope is impossible.
Moreover the claims relate to compounds which are actually not well-defined, namely "other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine or salts or carboxyl derivatives thereof" and " a second compound which is a positively charged compound or salts or carboxyl derivatives thereof" The claims cover all uses/compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such uses/compounds, namely referring to peptides that are coupled to radionuclides or metals. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the combination/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the uses/compounds disclosed in the examples and the compounds specifically identified by chemical name in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

International Application No
PCT/EP 00/06917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9104755 A	18-04-1991	AT 136224 T	15-04-1996
		CA 2066031 A	30-03-1991
		DE 69026387 D	09-05-1996
		DE 69026387 T	28-11-1996
		EP 0494247 A	15-07-1992
		JP 5500953 T	25-02-1993
		US 5648059 A	15-07-1997
		US 5380513 A	10-01-1995
WO 9746099 A	11-12-1997	CA 2257353 A	11-12-1997
		EP 0906015 A	07-04-1999
WO 9629087 A	26-09-1996	US 5843894 A	01-12-1998
		AU 700346 B	07-01-1999
		AU 5361696 A	08-10-1996
		CA 2190867 A	26-09-1996
		EP 0767673 A	16-04-1997
		JP 10505866 T	09-06-1998
EP 0747395 A	11-12-1996	US 5728678 A	17-03-1998
		CA 2177195 A	07-12-1996
		JP 9020678 A	21-01-1997